DEPARTMENT OF HEALTH AND HUMAN SERVICES

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February 6, 2004

ADVERSE DETERMINATION LETTER

BY FACSIMILE &
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Alan McCurry
Interim Executive Vice President and CEO
Biomedical Services
American National Red Cross
2025 E Street, N.W.
Washington, D.C. 20006

RE: United States v. American National Red Cross, Civil Action No. 93-0949 (JGP)

Dear Mr. McCurry:

This letter responds to the American National Red Cross's (ARC's) submission dated October 27, 2003, and hand delivered to the Food and Drug Administration's (FDA) Baltimore District on October 28, 2003, by ARC representatives. Your submission is ARC's response to FDA's July 22, 2003 Adverse Determination Letter issued to ARC under Paragraph VI.B. of the Amended Consent Decree of Permanent Injunction (Decree), entered on April 15, 2003. In that letter, FDA stated the bases for its determination that ARC failed to comply with Paragraph IV.B.1. of the Decree in the Problem Management standard operating procedure (SOP) it submitted on June 3, 2003. Paragraph IV.B.1. of the Decree requires that ARC establish and submit to FDA SOPs to detect, investigate, evaluate, correct, and monitor all problems, trends, and system problems.

Paragraph VI.B. of the Decree requires FDA to advise ARC in writing whether the revised Problem Management SOP, which consists of SOPs covering four areas -- policies, directives, work instructions, and reference materials -- appears to be adequate to bring ARC into compliance with the law and the Decree. FDA has reviewed the revised Problem Management SOP and has again determined that the revised Problem Management SOP continues to be inadequate to fulfill the requirements in Paragraph IV.B.1. of the Decree. Although ARC has corrected some of the deficiencies cited in the July 22, 2003 Adverse Determination Letter, FDA found that ARC still has failed to correct significant deficiencies. FDA has set forth below the bases for this determination:

1. The revised Problem Management SOP fails to comply with Paragraph IV.B.1. of the Decree (page 14), because it does not require that all trends be adequately corrected, and it does not include an adequate risk assessment procedure. The revised Problem Management SOP also fails to comply with Paragraph IV.B.1.a.ii. of the Decree (page 15), because it does not require each ARC region and

laboratory "...commensurate with the nature of the problem, [to] promptly, thoroughly, and adequately investigate, correct and take steps to prevent the recurrence of each problem...." Specifically, ARC's revised Problem Management SOP does not include an adequate risk assessment procedure and does not ensure that, commensurate with their nature, problems will be corrected to prevent their recurrence. For example,

a) Revised Problem Management SOP Work Instruction 10.3.2, "Assessing Risk" and Job Aid 10.4.ja2, "Biological Product Deviation Codes": The risk assessment procedure described in Work Instruction 10.3.2 is used by ARC to determine risk indicators, which in turn are used to "...determine the level of investigation and extent of corrective actions and preventive actions..." for problems. (See Bates page 030470.) To assist the regions and laboratories in assigning risk indicators, ARC has established a list in Job Aid 10.4.ja2 of Biological Product Deviation (BPD) codes that includes pre-assigned risk indicators to "assure that each problem will be addressed commensurate with the nature of its risk." (See Bates page 030549-030607.) Based on the directions in the Work Instruction and the Job Aid, ARC calculates risk indicators by [redacted] Job Aid 10.4.ja2 (at Bates page 030550) states, [redacted] However, neither the Job Aid nor the Work Instruction provides instructions to ensure that ARC regions and laboratories will consistently identify those situations and will properly recalculate the risk indicator in order to assign the appropriate priority to resolving such problems. Additionally, neither the Job Aid nor the Work Instruction provides instructions regarding recalculation of risk indicators based on factors such as frequency, duration, scope of problems, and distribution of unsuitable blood or blood products as a result of problems.

Because critical decisions regarding the extent of ARC's investigations and corrective actions will be based on risk indicators, it is important that the values listed in Job Aid 10.4.ja2 be reliably scored using appropriate criteria and that the scoring process used to develop the Job Aid be adequately controlled to ensure that values included therein are reliable. In its review of the Job Aid, FDA found that some problems were assigned risk indicators that appear to be too low or otherwise questionable. (See related questions and comments in item 2.a. through 2.e. on pages 7 and 8 of this letter.) For example, ARC has assigned risk indicators that deem the following types of problems as [redacted] donor safety problems (Bates page 030559); many of the donor screening problems (Bates pages 030560-030570); donor deferral problems (Bates pages 030575-030577); donor file check problems (Bates page 030565); hepatitis B, HTLV I/II, syphilis, and cytomegalovirus donor sample testing problems (Bates page 030588); and misbranding problems, such as products not meeting leukoreduction criteria labeled as leukoreduced and antigen-positive products labeled as antigen-negative (Bates page 030592).

b) Revised Problem Management SOP Work Instruction 10.3.3," Investigating Problems" and Revised Problem Management SOP Work Instruction 10.3.4, "Developing Corrective Action Plans and Effectiveness Checks": In Work Instruction 10.3.3, ARC established [redacted] levels of investigations that it believes are commensurate with the level of risk posed by problems. Specifically, the Work Instruction designates [redacted] Work Instruction 10.3.3 requires that investigations for [redacted] problems include determining the probable cause, correcting the problem, documenting the rationale in the

automated problem-management system, and forwarding to QA for closure. (See Bates page 030478, item 8.) Work Instruction 10.3.4 only requires development and implementation of a thorough corrective action to prevent recurrence of [redacted] (See Bates page 030480.) Work Instruction 10.3.4 does not provide any information regarding which [redacted] It also fails to direct ARC regions and laboratories to develop and implement corrective actions to prevent recurrence of [redacted] problems that are identified as trends. (Paragraph III.B.64 of the Decree (page 10) defines a trend as "the recurrence or multiple contemporaneous occurrences of the same or similar problems in one or more than one ARC region and/or laboratory.")

At Bates page 030478, Work Instruction 10.3.3 asks in item 12, [redacted] The Work Instruction should state clearly that such a "no fault" determination must be based not only on review of the circumstances of an individual problem but also on trending information for similar problems. Few, if any, of the problems related to ARC's manufacture of blood and blood products should be regarded as [redacted] For example, the Work Instruction mentions post-donation information as a type of problem beyond ARC's control. Although it is true that a donor's failure to provide information relevant to required deferral from donation may be beyond ARC's control, a trend of increasing post-donation information reports should trigger an ARC investigation to determine whether there is a problem with health historian interviews or a problem related to a particular blood donation record question. Such circumstances are within ARC's control, and ARC is obligated to identify, correct, and prevent recurrence of those problems.

In item 2 of the July 22, 2003 Adverse Determination Letter, FDA stated that ARC's Problem Management SOP submitted on June 3, 2003, failed to comply with Paragraph IV.B.1.a.ii. of the Decree because it provided instructions to categorize problems and to only investigate, correct, and prevent categories of problems. ARC has not fully addressed that failure in this revised Problem Management SOP. Instead, the revised Problem Management SOP requires an investigation of all problems, but does not require that they be corrected in a manner to prevent recurrence. Although FDA accepts the approach that genuinely "minor" risk [redacted] problems may be, in addition to logged and tracked, corrected without use of a formal corrective action plan (as defined in the revised Problem Management SOP), FDA fully expects ARC to ensure reliable and accurate risk assessment and to implement corrective actions that prevent recurrence of the problems that are identified as trends by a region, laboratory or BHQ.

c) Revised Problem Management SOP Work Instruction 10.3.4, "Developing Corrective Action Plans and Effectiveness Checks": Work Instruction 10.3.4 requires a [redacted] However, the Work Instruction provides no indication of what types of [redacted] problems trigger a directive by ARC to develop and implement a [redacted] corrective action. (See Bates page 030480.) In addition to thoroughly correcting and preventing recurrence of [redacted] problems, FDA expects ARC, at a minimum, to thoroughly correct and prevent recurrence of all trends related to [redacted] problems.

As stated above in item 1.a on page 2 of this letter, FDA finds that reliance on Job Aid 10.4.ja2 to determine a risk indicator, which is then used, according to Work Instruction 10.3.4, to determine the

extent of corrective actions, may result in ARC's failure to prevent recurrence of potentially significant problems.

Additionally, FDA finds that the time frames for completion of corrective action plans, as defined on Bates page 030615, listed in Work Instruction 10.3.4 (at Bates page 030480 through 030482) fail to comply with the Decree requirement "commensurate with the nature of the problem...[to] promptly... correct, and take steps to prevent the recurrence of each problem...." For example, the Work Instruction allows 90 days to complete corrective action plans for [redacted] and 150 days for [redacted] problems. (See Bates pages 030482.) FDA finds unacceptable a policy that allows longer time frames for completion of corrective action plans for all [redacted] problems than for lower risk problems. ARC must give a higher priority to expeditious resolution of "major" risk problems.[1]

Additionally, (at Bates page 030484) step 9 of Work Instruction 10.3.4 directs the regions and laboratories to assign a new problem number when the effectiveness check indicates that a problem was not solved, following the implementation of the corrective action plan. Although Directive 10.2.1, "Problem Management" (at Bates page 303443), requires linkage of a new problem number to an "existing" problem number for unresolved problems, there is no assurance that all previously assigned numbers will also be linked. In order for ARC and FDA to readily evaluate the adequacy of prior investigations and corrective actions related to unresolved problems, ARC must clearly link all numbers previously assigned to a problem that remains unresolved after ARC implemented multiple ineffective corrective actions.

2. The revised Problem Management SOP fails to comply with Paragraph IV.B.1.b., because it is not designed to adequately identify trends. (Paragraph III.B.65 of the Decree (page 10) defines a trend as "the recurrence or multiple contemporaneous occurrences of the same or similar problems in one or more than one ARC region and/or laboratory.") For example (at Bates pages 030528 to 030533), the revised Problem Management SOP Work Instruction 10.3.13, "Identifying Trends," requires use of [redacted] to identify trends in a single facility and [redacted] to identify system-wide trends. The revised SOP does not provide sufficient information regarding limits and use of [redacted] Although FDA acknowledges that [redacted] may be used for trending, it sees limited applicability in the manufacture of blood and blood products, particularly when use of those charts may result in ARC's acceptance of a level of non-compliance with the law, ARC SOPs, or the Decree. For example, [redacted] are not an appropriate trending mechanism if used in a manner that results in establishing an acceptance limit for lost blood products because the law clearly requires that the disposition of each blood product must be traceable. (See 21 CFR § 606.165(a).) Moreover, such problems must be trended in a manner that requires more detailed analyses than that required by either chart. Such analyses should include, but are not limited to: 1) a review of the number of

[1] FDA also notes that the time frames set forth in Work Instruction 10.3.4 appear to be inconsistent with the requirements of Paragraph X.F. of the Decree (Page 65). Paragraph X.F. requires ARC "...within 10 days of initially discovering a problem that may result or may have resulted in the release for distribution of units of unsuitable blood or blood components, to review and document the review of all records necessary to determine whether distribution of units of unsuitable blood or blood components in fact occurred and to identify all related units of unsuitable blood or blood compouents that were, may have been, or may be distributed...." While the Work Instruction does mention (at Bates pages 030474 and 030475) determining whether other blood products have been affected and notification of consignees, it does not refer to the 10 day time frame for the Decree requirement above.

problems reported by regions and laboratories; 2) a review of root causes determined by regions and laboratories; 3) an evaluation of the appropriateness of corrective actions implemented by regions and laboratories; and 4) an evaluation of the significance of the individual problems being analyzed, including whether unsuitable blood products have been released.

3. The revised Problem Management SOP fails to comply with Paragraph IV.B.1. of the Decree, because it does not ensure that each region and laboratory will "detect, investigate, evaluate, correct and monitor all problems,[2] trends, and system (systemic) problems" reported through external complaints. FDA notified ARC in item 1 of the July 22, 2003 Adverse Determination Letter that the Problem Management SOP ARC submitted on June 3, 2002, was deficient in this respect. FDA has determined that your revised Problem Management SOP does not correct that deficiency, because Work Instruction 10.3.11, "External Customer Complaint Management," only provides instructions for handling direct complaints directly related to a product, not complaints relating to process, procedures or employee performance.

4. Work Instruction 10.3.9, "Suspension of Activities," provides instructions for reporting suspension of activities. (See Bates Pages 030511 through 030513.) However, those instructions do not comply with the requirements for reporting partial or complete suspensions in Paragraph XIX of the Decree. In Work Instruction 10.3.9, the criteria for reporting suspension of operations are "completely stopped activity for 24 hours or more, or partially suspended (work slow down) for 24 hours or more because of any compliance issue." However, the Decree states that "ARC shall take all actions necessary to accomplish the objectives of this Order, including personnel actions...and partial or complete suspension of operations of one or more regions and/or laboratories. ARC shall notify FDA within 24 hours of any such suspensions of operations...." ARC is required to notify FDA of all partial or complete suspensions of operations. To ensure compliance with Paragraph XIX, FDA expects ARC to revise all other references to the partial or complete suspensions of operations in the revised Problem Management SOP, such as the Job Aid: Glossary of Terms, found at Bates page 030617.

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In addition to the deficiencies cited in items 1 through 4 above, FDA's review of ARC's revised Problem Management SOP revealed additional problems that raise serious questions about its adequacy and about ARC's compliance with other provisions of the Decree. Therefore, FDA has the following comments and requests for additional information:

1. Work Instruction 10.3.10, "Managing Material Review Boards," provides instruction for determining the disposition of non-conforming materials, including distributed blood products. It

[2] In its entirety, the definition of "problem" in the Decree is "any deviation from the law, ARC SOPs, or this Order, however discovered, recorded, or reported, including, but not limited to deviations reported in ARC Clarify reports (and/or in any other successor or similar deviation-reporting systems and/or reports), biological product deviation reports, internal deviation reports, trends, adverse reaction reports, lookback cases, cases of suspected transfusion-transmitted disease, potential system (systemic) problems, system (systemic) problems, supply and equipment problem reports, FDA 483s, compliance-related FDA correspondence, internal and external audit reports, and retrievals."

instructs the quality assurance (QA) staff to check ARC's [redacted] to determine whether a precedent case exists and, if so, "disposition the products according to the precedent case, approve, and close...." However, the Work Instruction does not direct the QA staff to use current standards to evaluate the precedent case, prior to deciding whether to retrieve unsuitable blood products from the marketplace. For example, precedent actions taken early in the evaluation of the white particulate matter found in donor bags may or may not be appropriately applied to more recent occurrences. ARC must ensure that QA staff not only consult the [redacted] but also consider all available relevant information to determine whether to retrieve distribute unsuitable blood products. The Work Instruction only provides for periodic review of [redacted] precedent cases and quarterly updates of the [redacted] with results of those periodic reviews. Given its use of the [redacted] in making critical decisions, ARC should establish a required frequency for its review of [redacted] precedent cases.

2. FDA requests the following additional information related to Job Aid 10.4.ja2, "Biological Product Deviation Codes, which is found at Bates pages 030549-030607:

a) Please explain the inconsistent risk indicators and [redacted] ratings for BPD codes LA-81-12, "irradiation status incorrect or missing," and BPD code LA-81-14, "irradiation and leukoreduction status incorrect." (See Bates page 0300592.) Also explain why BPD code LA-81-14 is assigned a risk indicator of [redacted], while at Bates page 030550, the [redacted] states that when a blood product is labeled as irradiated, but irradiation was not performed, the problem will be tracked as high risk no matter what the circumstances. Additionally, at Bates pages 030603, ARC's rationale for the [redacted] is that "product not irradiated..." will always receive "a high [redacted] rating regardless of the circumstance." However, QC-97-02 "product not irradiated" is assigned a [redacted]. Please explain this discrepancy.

b) FDA classified 594 ARC recalls in 2003. Of that number, 144 were ARC recalls associated with donor screening (DS) BPD codes. ARC has assigned a [redacted] to many of its DS BPD codes because the problems are "[redacted]." (See Bates page 030471.) If DS errors are easily detectable, please explain why ARC did not detect DS problems that led to the 144 recalls in 2003.

c) At Bates page 030565, ARC has assigned a [redacted] for BPD code DS-26-01-04, "donor file check, search incorrectly completed" because "[redacted]." Since the purpose of donor file check is to search ARC's [redacted] and, when applicable, [redacted] for previous donations from a now-deferred donor, the stated rationale for the [redacted] does not appear applicable to donor file check. Please state what procedures ARC has established for review of donor file check searches that justifies a [redacted]

d) At Bates page 030588, ARC has assigned the [redacted] for "testing performed incorrectly for" hepatitis B (surface antigen) and cytomegalovirus (CMV) because "[redacted]." However, hepatitis B may have long term effects on the liver, such as cirrhosis, liver failure, or hepatocellular carcinoma. CMV may cause death in infants and may result in serious health consequences for immunosupressed patients. Please explain ARC's rationale for assigning a [redacted]

e) At Bates page 030592, ARC assigned [redacted] for BPD code LA-82-08-01, "antigen-positive unit labeled as antigen-negative." The product would be misbranded, and consignees generally do not re-check the antigen status. Such misbranded products could present a serious risk to recipients. Please explain ARC's rationale for assigning a [redacted]

3. FDA found that the revised Problem Management SOP is inconsistent and will not assure development and implementation of thorough corrective actions for all trends detected at BHQ that involve [redacted] problems. Specifically, although Work Instruction 10.3.4 (at Bates page 030480) states that [redacted] corrective action plans are required for escalated or systemic problems and problems identified in the Analysis and Investigation Report (required under Paragraph IV.B.1.b. (page 17), Directive 10.2.3, "BHQ Management of Problems," which addresses managing problems identified in the Analysis and Investigation Report, provides directions to follow Work Instructions 10.3.3 to determine the extent of investigative activities. (See Bates page 030463.) In turn, Work Instruction 10.3.3 allows [redacted] problems to be closed without a [redacted] corrective action. Therefore, a user following the instructions in Directive 10.2.3 and Work Instruction 10.3.3 may conclude that no [redacted] corrective action is necessary to prevent problems identified as a trend involving [redacted] problems.

4. FDA acknowledges that ARC's revised Problem Management SOP states (on Bates page 030419) that [redacted] For that reason, FDA verbally asked ARC to provide several procedures that ARC referenced in the revised Problem Management SOP. ARC provided those procedures on December 1 and 11, 2003.

FDA's review of the procedures shows that ARC has not sufficiently reviewed, revised, and fully integrated all of them into the Problem Management SOP to ensure compliance with the Decree. FDA is particularly concerned with those procedures for reports that Paragraph IV.B.1.a. of the Consent Decree requires to be scrutinized by ARC for the purpose of problem identification -- specifically, internal deviation reports, including "hotline" reports, Clarify reports, and computer-software and hardware problem reports. The following examples illustrate the need for review and revision of these related procedures:

a) LOP 90.800, [redacted] Version 1.0, Version Date: April 17, 2003, provides instructions for the investigation, resolution, and documentation of calls to the [redacted] FDA's review found that procedures for entering hotline cases into the [redacted] (on page 6 of LOP 90.800) are incomplete because no instructions are provided for entering information, including problem type, discovery information, function, and source code, into the [redacted] as required by Job Aid 10.4.ja7. Additionally, page 6 of LOP 90.800 states that hotline problem description entered into [redacted] If by this ARC means that scarce detail will be entered into the [redacted] description field, FDA is concerned that some hotline problems may be overlooked during trending and trend analysis. Finally, to ensure that hotline problems are managed in accordance with the Problem Management SOP and Decree, ARC should also revise the LOP to provide clear instructions regarding who is responsible for determining which hotline

reports are problems that must be logged and tracked in [redacted] and who is responsible for investigating and correcting those problems, in accordance with Paragraph IV.B.1 of the Decree.

b) At Bates Page 030462, the Problem Management Procedures refer the user to BSD 23.110M, "Process for User Support and Software Releases," for criteria to identify ARC-supported computer software and/or hardware-related adverse trends and problems that must be elevated to BHQ. However, FDA's review of BSD 23.110M (Version 1.1, Version Date: November 2000) showed the procedure lacks such criteria.

c) BSD 23.111, "Problem Reporting and Tracking," Version 1.0, Version Date: December 2000 is ARC's procedure for tracking calls received from regions and laboratories through the "Clarify" call tracking system. That tracking system is separate from [redacted] FDA's review of BSD 23.111 shows that it does not provide instructions to ensure that problems reported through the Clarify system by regions and laboratories will also be entered into [redacted] BSD 23.111 also does not provide instructions to ensure that issues reported by regions and laboratories through Clarify and, subsequently identified at BHQ as problems, will be entered into [redacted]

The list of ARC procedures requested by FDA is not an all-inclusive list of those that support or relate to the Problem Management SOP, and items 6.a. 6.b., and 6.c. above are not intended to represent an all-inclusive list of inconsistencies or potential deficiencies. ARC should review all related and supporting procedures and revise them as necessary to ensure integration with the Problem Management SOP and compliance with the Decree. Additionally, ARC should determine whether additional supporting procedures must be established, such as procedures outlining the means by which, the frequency of, and the person(s) responsible for review of FDA 483 observations and FDA compliance-related correspondence to identify problems and to ensure those problems are promptly entered into ARC's tracking system.

* * *

Paragraph VI.B. of the Decree provides that if FDA determines that any SOP, report, or plan submitted under specified paragraphs of the Decree, including Paragraph IV.B.1., "appears inadequate, FDA shall state the specific basis for its determination in writing, and the penalty, review, and appeal procedures set forth in Paragraph IX below shall be followed until ARC obtains a favorable determination from FDA or the Court as to the apparent adequacy of that SOP, report, or plan." Paragraph VIII of the Decree provides that if FDA determines that ARC "has failed to fully comply with any...term, or provision of this Order" or "that any report, plan, SOP, or other measure implemented by ARC to comply with this Order is inadequate to comply with the law,..., or this Order; then FDA may order ARC to come into compliance with the law, ..., or this Order, assess penalties, and/or to take any step that FDA deems necessary to bring ARC into compliance with the law, ARC SOPs, or this Order."

For the reasons stated above, FDA has determined that the ARC's revised Problem Management SOP is inadequate to comply with the law and the Decree, that the violations are significant, and that it should invoke the penalty provisions of the Decree. Indeed, as explained elsewhere in this letter, the omissions in ARC's SOP are, in most cases, explicitly required by specific language in the Decree. In other cases, FDA has brought the particular deficiencies to ARC's attention in the July 22, 2003 Adverse Determination Letter, previous FDA 483s and VI.A. letters. Finally, ARC has been on notice for several

years not only as to many of the specific deficiencies in this revised SOP, but also that FDA regards this SOP as a first and indispensable step to enable ARC to comply with current good manufacturing practice. In the revised Problem Management SOP, ARC has corrected some deficiencies in the previous SOP; however, the revised SOP falls significantly short of compliance with the Decree.

FDA hereby orders ARC to revise the Problem Management SOP in a manner that will correct the violations discussed above and otherwise comply with the law and the Decree. Pursuant to Paragraph IX of the Decree, FDA intends to fine ARC $7,500 for 60 days of the period between October 28, 2003, and February 6, 2004. Please note that this period does not include the period between the date of this letter and your next submission. (See Decree Paragraph IX.) If the next version of the Problem Management SOP is inadequate and a fine is imposed, the fine would include the preceding period.

As provided in the Decree, if ARC agrees with this adverse determination, it shall within 20 days of receipt of this letter, notify FDA of its intent to come into compliance with the Decree and submit a plan to do so. If ARC disagrees with FDA's adverse determination, it shall respond in writing within 20 days of receipt of this letter, explaining its reason for disagreeing with FDA's determination. Your response must be submitted to me at the Food and Drug Administration, Baltimore District Office, 6000 Metro Drive, Suite 101, Baltimore, Maryland 21215, with a copy to Jesse Goodman, M.D., Director, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852.

Sincerely,

Lee Bowers
Director, Baltimore District

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